E.T. Howell

Studies in the Heterocylic Series

STUDIES IN THE HETEROCYCLIC SERIES

BY

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THESIS

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY Edward Tillson Howell

ENTITLED Studies in the Heterocylic Series

BE ACCEPTED AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE DEGREE OF Master of Science

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on
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*Required for doctor's degree but not for master's

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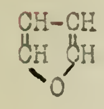
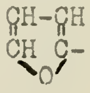
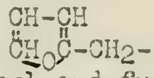
STUDIES IN THE HETEROCYCLIC SERIES

I. INTRODUCTION

Although members of the heterocyclic series of compounds exist, which are entirely analogous to aromatic compounds, the heterocyclic amine, furyl amine, corresponding to aniline, has never been isolated. It is the purpose of this paper to describe attempts made to prepare this compound and to study some of the important reactions involved in the various steps of the work. In the present thesis the following topics are taken up: further improvement in the preparation of pyromucic acid; further investigation of the Hofmann hypobromite reaction; the synthesis of bromofurane and a study of reactions involved; and the Ullmann reaction as applied to the latter compound.

The work undertaken here is a continuation of that done in 1918-1919, in which a method was worked out for the preparation of pyromucic acid, and in which the effect of the Hofmann hypobromite reaction on pyromucic acid amide was studied.

Nomenclature. The five membered heterocyclic compound  is known as furane or furfurane (1), while the group  is referred to as furyl, and the group  as furfuryl. In the literature the terms furyl and furfuryl are frequently used interchangeably, causing some confusion. However, the most common usage reserves "furfuryl" for those compounds having a side-chain carbon.

agents were all tried: aluminum amalgam; zinc and acetic acid; zinc and sodium hydroxide; ferrous sulphate and ammonia; pyridine, acetic acid and zinc; acetic anhydride, acetic acid and zinc. No amino furane was obtained, the reduction products being aldehydic in nature, indicating hydrolysis of the furane nucleus. In regard to the second method, the furyl urethane when treated with alkali decomposed completely forming open chain compounds. The last method seemed to be the most promising.(6) Ethyl pyromucate was nitrated in a special manner giving beta nitro pyromucic ethyl ester which was saponified to the corresponding acid. On reduction this nitro acid yielded the amino acid. To eliminate the carboxyl group, the acetyl derivative of the amino acid was heated in a sealed tube with pyridine at 170°-180°, which gave the acetyl derivative of beta amino furane together with carbon dioxide. However when a hydrolysis was attempted either with acid or alkali solutions to get the free furyl amine, the compound was completely decomposed with the formation of open chain substances.

In looking over the various papers by Marquis, it seems rather peculiar that hardly any mention is made of Freundler's work which is referred to in but one or two instances; and yet Freundler claimed to have prepared a small amount of substance (from the urethane) which he evidently thought might be the amine so long sought for. The fact that the simultaneous work of Curtius-Leimbach (8) and Marquis on the hydrolysis of the urethane gave no amine makes it seem improbable that Freundler's compound boiling at 150° was the amine.

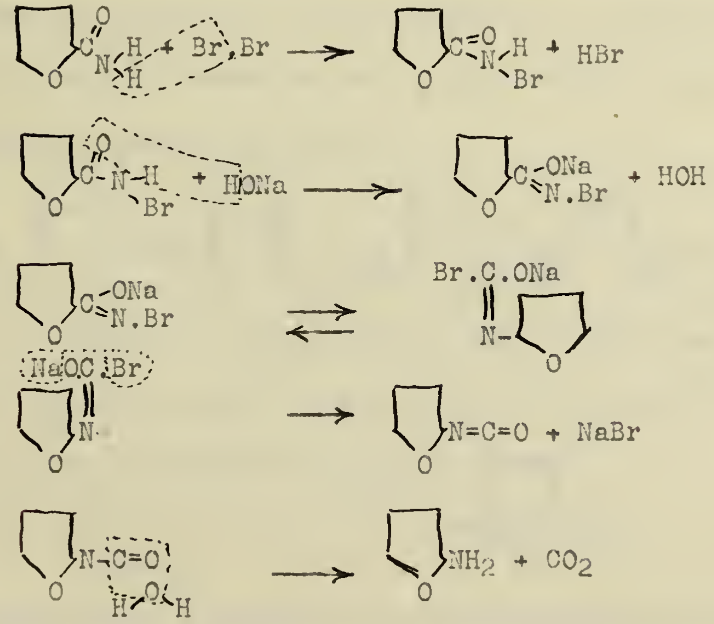
Work of Curtius and Leimbach. (8) These men prepared the furyl urethanes $C_4H_3O.NH.COOMe$ and $C_4H_3O.NH.COOEt$ from the azo imide

and the corresponding alcohol in the hope that upon hydrolysis the amine would be obtained. The authors say, "All attempts to prepare furyl amine from the urethane failed."

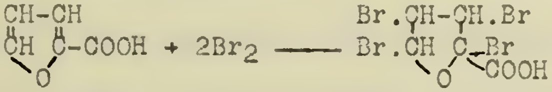
From the foregoing resume it appeared as if both the alpha and beta furyl amines are incapable of existing in the free state. The only course open was to try the Hofmann reaction under different conditions than those used by Freundler, or to try a synthesis entirely different from any of those previously used.

III. THEORETICAL PART

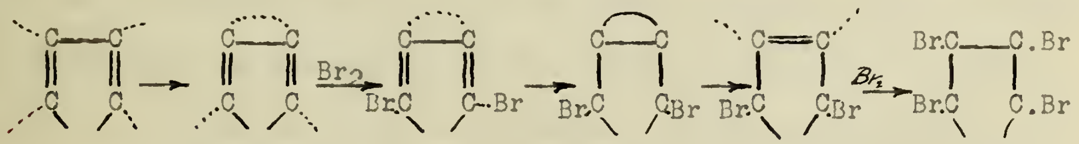
1. The Hofmann Hypobromite Reaction. If pyromucic acid amide behaves like a typical amide, the mechanism of the hypobromite reaction according to Weyl, would be as follows:



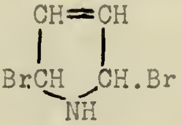
2. Tetrabrom Pyromucic Acid. The formation of this compound involves the simple addition to double bonds. In this case the furane ring shows itself to be aliphatic in character. However there are small amounts of substituted products formed simultaneously with the addition product, since HBr is evolved to some extent. This is what we would expect if the ring were entirely benzenoid in character. If bromine is added to a solution of pyromucic acid in glacial acetic acid, a mono brom pyromucic acid can be obtained. This is a replacement of hydrogen and is entirely analogous to the bromination of benzene. The addition reaction is represented as follows:



The ring contains the conjugated system -C=C-C=C-, and if it behaves like aliphatic compounds containing the same linkage, the prediction would be that a dibrom addition product would be formed as an intermediate compound in the preparation of tetrabrom pyromucic acid. If this were expressed according to Thiele's theory, the addition would take place somewhat as follows:



As evidence that this intermediate compound may exist, there is the analogous case of the bromination of pyrrol, which takes place giving the dibrom derivative



3. Formation of Beta-Gamma and Beta-Delta Dibrom Pyromucic Acids. These are made by treating tetrabrom pyromucic acid with alcoholic NaOH, when a mixture of the sodium salts of the two dibrom acids is

[illegible]

[illegible]

$$[illegible]$$

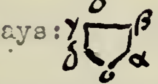
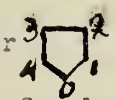
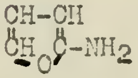
[illegible]

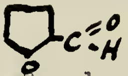
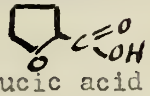
$$[illegible]$$

[illegible]

$$[illegible]$$

[illegible]

For the sake of convenience the ring is often written ,  or . The carbon atoms are designated in the following ways: ,  or . Thus  $\begin{array}{l} CH{-}CH \\ \overset{\|}{C}H_{O}\overset{\|}{C}{-}NH_2 \end{array}$ would be called alpha furyl amine or 1-furyl amine.

Some derivatives are  

Furfural Pyromucic acid
(Furane 1-carboxylic acid)

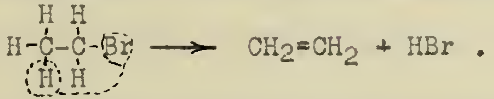
II. HISTORICAL PART

Of the many attempts which have been made to synthesize furyl amine (1 or 2), none have succeeded with possibly one exception. The largest amount of work in this connection has been done by Freundler in 1896-1897, and Marquis in 1901-1905.

Freundler's Work. (2) Freundler proposed three methods for preparing furyl amine: (a) the Hofmann reaction on the acid amide, (b) the hydrolysis of furyl urethane, and (c) the reduction of nitro furane. He gave very few details regarding the Hofmann reaction, merely stating that it was run at about 70° and that the mixture became alkaline with ammonia, accompanied by the formation of nitrogen and carbon dioxide. In reference to the second method, Freundler claimed that he got a few drops of a substance boilng at 150°, but finally abandoned this method in favor of the last one. However, no reference could be found dealing with the reduction of nitro furane to the amine.

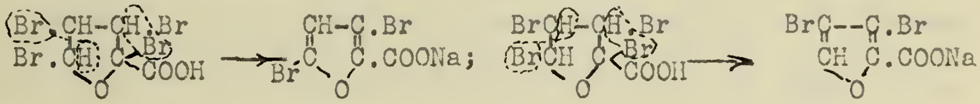
Work of Marquis. (3) Marquis also tried three methods for preparing furyl amine: (a) reduction of nitro furane (4), (b) the hydrolysis of furyl urethane (5), and (c) the decarboxylation of amino pyromucic acid (6). In the first method the following reducing

formed. (See Experimental Part.) The reaction is analogous to the formation of ethylene by treating ethyl bromide with alcoholic NaOH in which there is a splitting out of HBr accompanied by the formation of a double bond.

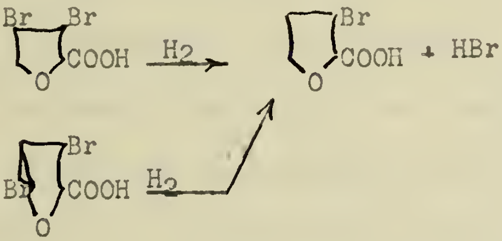


$$H-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-Br \longrightarrow CH_2{=}CH_2 + HBr \, .$$

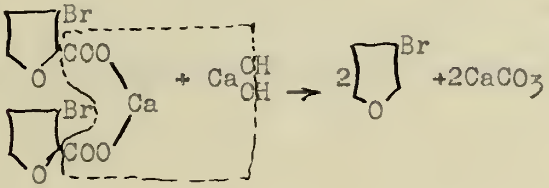
In the case of the tetrabrom pyromucic acid however there is a chance for HBr to split out in several ways, hence a mixture of two different dibrom pyromucic acids is formed, using three moles of NaOH per mole of acid.



4. Beta Monobrom Pyromucic Acid from Dibrom Pyromucic Acids. In this reaction there is a splitting off of HBr by reduction, replacing one Br atom with hydrogen.



5. Beta Brom Furane from Beta Monobrom Pyromucic Acid. This step is analogous to the formation of a hydrocarbon, RH, by splitting off CO_2 when the sodium salt of the corresponding acid is distilled with soda-lime. ($R.COONa + NaOH \rightarrow RH + Na_2CO_3$.)



6. Formation of Amines from Halogen Compounds. The stability of the halogen atom attached to the benzene ring has been of consider-

able interest because it has prevented until recently the direct synthesis of aromatic amino compounds from the halogen derivatives of the aromatic hydrocarbons. The early investigators failed entirely in their efforts to replace the halogen by other groups. It was not until 1914 that Meyer and Bergious (9) reported that ammonia converts chlorobenzene partly into aniline when heated at about 200°.

In 1903 Ullmann accidentaly made the discovery that metallic copper had a strong labilizing effect on the nuclear halogen (10).

Quick (11) has recently prepared aniline from chlorobenzene by heating it in a steel bomb with aqueous ammonia and copper salts. He gives the following results:

Ammonia used	Temperature	Yield of Aniline	Catalyst
150cc (25%)	195°	16g (39%)	$CuSO_4$
150 (27)	230	16 (39)	CuCl

Since it has already been pointed out that the furane ring is partly aliphatic and partly aromatic, and since halogen derivatives of aliphatic hydrocarbons are easily attacked by ammonia, it was thought likely that the bromine atom of brom furane might readily be replaced in the same manner by an amino group, especially if influenced by a catalyst such as powdered copper.

If this reaction did take place, there is the possibility of another one also occuring; namely, the possibility of the formation of a pyrrol derivative by the replacement of the oxygen in the ring by an imide group. This is plausible since pyrrol can be prepared from pyromucic acid by distilling with zinc-ammonium chloride and CaO. (12).

IV. EXPERIMENTAL PART.

1. Pyromucic Acid. Pyromucic acid was prepared by alkaline oxidation of furfural. One mole of furfural, 2 moles of calcium hydroxide, 25cc of ether, and 1 liter of water are placed in the 5-liter flask "A", which is cooled to about 0° by the ice-salt mixture in "D", and which is fitted with mechanical stirrer "C" and dropping funnel "B". A saturated solution (about 2500 cc) of 2/3 of a mole of $KMnO_4$ is then added in a rapid succession of drops. When all the permanganate has been added the stirring is continued for a few minutes, after which the flask is removed and heated on the water bath until the oxides of manganese have coagulated somewhat. After this precipitate is filtered off, the clear solution of calcium pyromucate having a volume of about 3500cc is evaporated with bone black to a volume of about 250 cc, and filtered.

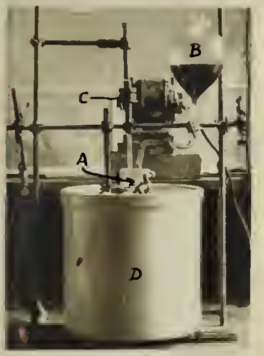


Fig. 1.

It was found that by treating the calcium salt with bone black a very much clearer solution is obtained, and also upon acidification with concentrated HCl the resulting pyromucic acid is white instead of buff colored.

The same method as the above was tried omitting the addition of ether, with the following results:

Method	Yield	Per cent of theory	M.P.	Pure acid.
With ether	65g	58%	125-130°	132-134°
Without ether	57g	51%	129-130°	

The amount of ether added is just enough to dissolve in the water used. Its effect seems to be that it aids in taking the furfural into solution in the water.

2. Pyromucyl Chloride. The method of Baum was used (13).

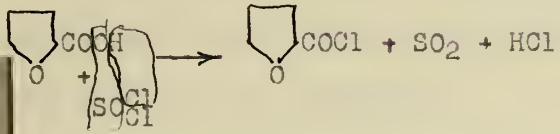



Fig.2.

One part of pyromucic acid is treated with five parts by weight of thionyl chloride, $SOCl_2$. The mixture is refluxed 1 to 2 hours on a water bath. The reflux condenser must be connected to bottles containing caustic, as shown in Fig. 2, to absorb the SO_2 and HCl evolved. The greater part of the thionyl chloride is then distilled off, coming over at 75° to 90°, and when the temperature starts to rise, the receiver is changed and the distillate collected which comes over around 173°.

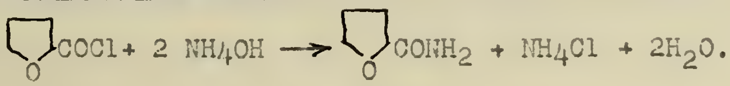
It was found that refluxing 1 to 2 hours is too long, as a solid decomposition product forms. 1/2 to 1 hour gave much better results.

As pyromucyl chloride is extremely irritating to the eyes, it must be handled cautiously, and the redeiver for collecting it should be closed as shown in Fig. 3.


Fig. 3.

No difficulty was experienced in making the acid chloride in this manner in 40 gram lots. The yield is almost quantitative. This method is much to be preferred to that using PCl_5, as there are no solid or liquid by-products, and much better yields are obtained.

3. Pyromucic Acid Amide.

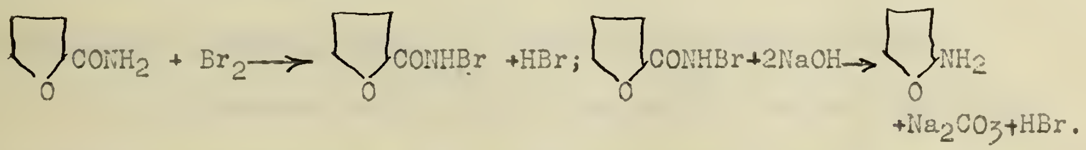


Both of the above reactions were carried out. The method is simply to add the acid chloride drop by drop with cooling to a solution of ammonium hydroxide or carbonate.

70-75% yields of the amide were obtained using ammonium hydroxide, while 85% of the theoretical amount of amide was obtained using ammonium carbonate solution. The amide obtained by this method was pure enough to use without recrystallizing, the melting points varrying from 137° to 141°, the M.P. of the pure compound being 140°-141°.

4. <u>The Hofmann Hypobromite Reaction</u>. Since Freundler carried out his Hofmann reaction at about 70° and obtained no amino furane, it was decided to try the same reaction at room temperature or even lower.

The method used was to dissolve bromine in NaOH solution forming NaOBr which was added in portions with cooling to an aqueous or alkaline solution of the pyromucic amide, allowing it to stand, and then examining the products of the reaction. The proportions used were one mole of available Br_2 per mole of amide, which would correspond to the theoretical reaction:



In the first two runs the reaction mixture was steam distilled giving a water white distillate which was alkaline to litmus and which had a strong odor of ammonia. It was acidified with HCl and evaporated to dryness in order to obtain the amine hydrochloride if present. A white residue was obtained which, however, proved to be ammonium chloride.

It was thought that steam distillation might have caused hydrolysis of the amine (if it formed at all) so it was decided that in the next run, the reaction mixture would be extracted with ether in the cold instead of subjecting it to such vigorous treatment as steam distillation. The ether extracts from the next few runs were evaporated on the water bath, but in no case was there any appreciable residue left.

These facts lead one to believe that it is not likely that the amine, if it exists, can be prepared by the Hofmann reaction. The amounts of pyromucic amide used in these runs were 10 grams.

In all of the above trials, it was noticed that there was a slight evolution of gas when the hypobromite solution was added to the amide solution. In order to determine the nature of the gas, an apparatus as shown in Fig. 4 was used. The amide solution in "A" was treated with the NaOBr soltuin run in from "B", and the gas collected in "C". Tests showed that it was not NH_3 or CO_2, but is probably nitrogen from the oxidation of ammonia by the hypobromite.

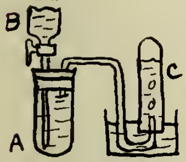


Fig. 4.

5. Tetrabrom Pyromucic Acid. The method of Hill was used.(14)

Dry pyromucic acid and dry bromine are placed side by side in dishes in a desiccator, in the proportions of 1 mole of the former to 4 gram atoms of the latter. After about 24 hours the bromine disappears, while the pyromucic acid changes to a voluminous mass with an increase in weight corresponding to the bromine added. The main reaction is one of addition as explained in the Theoetical Part. However a considerable amount of HBr is evolved, indicating replacement of hydrogen as well as addition.

Upon standing in the air, the tetrabrom acid so prepared loses any excess of bromine vapors which may be mechanically contained. It need not be purified for the next reaction.

10 and 20 grams of pyromucic acid were used giving slightly less than the theoretical yield of tetrabrom pyromucic acid, 38 and 76 grams respectively.

6. Dibrom Pyromucic Acid. Method of Hill. (15)

Powdered tetrabrom pyromucic acid is slowly stirred into concentrated alcoholic NaOH with the temperature kept below 25° with an ice bath. The proportions used are 1 mole tetrabrom acid to 3 moles of NaOH, one of which neutralizes the carboxyl group, leaving two to split out two Br atoms in the form of NaBr. The sodium salts of beta-gamma and beta-delta dibrom pyromucic acids and NaBr form immediately. These are filtered off, then dissolved in water and acidified with conc. HCl, whereupon a mixture of the two dibrom pyromucic acids separate out. These are filtered off and dried.

Hill gave 136°-138° as the melting point of this mixture, with a yield of about 35%. The mixture of the two acids in this work was found to melt at 133.5°-136° after one recrystallization. Yield 30%.

When the tetrabrom pyromucic acid was treated with NaOH with a consequent splitting out of HBr, it was decided to follow the course of the reaction to determine if it went by steps, that is, to determine whether one bromine atom was attacked more readily than another. The method used was as follows: A number of 0.2 gram samples of tetrabrom pyromucic acid were weighed out and dissolved in water. Enough 0.1 normal NaOH solution was added to the first sample

to furnish three moles NaOH to every mole of the tetrabrom acid, and any excess of NaOH was then titrated immediately with standard HCl solution. The same was done with sample No. 2, except that an interval of 5 seconds was allowed before the NaOH was titrated. The same procedure was used on each succeeding sample, except that the action of the NaOH was allowed to continue five seconds longer than with the preceding sample.

It was anticipated that 1/3 of the NaOH would be immediately used up in neutralizing the carboxyl group, and that one third would be used up more slowly in attacking the most reactive Br atom, while it was expected that the less reactive Br would be attacked less rapidly by the remaining NaOH. If such conditions held, a graphic representation would be somewhat as shown in Fig. 5. However, what was actually found to be the case was that all the NaOH was used up in one or two seconds, or almost instantaneously. This shows that the alpha, gamma, and delta Br atoms are of nearly the same reactivity.

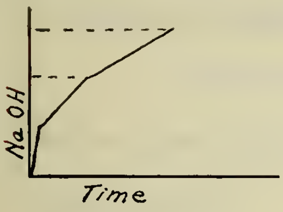


Fig. 5.

7. Beta Monobrom Pyromucic Acid. Hill's Method (16)

2 parts of dibrom pyromucic acid (from above method) are dissolved in 6 parts of water, and 6 parts of aqua-ammonia. 1 part of zinc dust is then added slowly with cooling. The reaction takes place almost immediately and is complete in a short time. After filtering off the excess zinc the solution is acidified with HCl, giving a buff-colored precipitate of beta brom pyromucic acid which is filtered off and dried. Zinc with ammonia is a weak reducing agent. A stronger one can not be used since the beta bromine atom

as well as the gamma or delta might be reduced. The beta seems to be the more stable toward reduction. A yield of 20% was obtained, the product melting at 125°-128° after one recrystallization. Hill gives 128°-129° as the melting point.

8. Beta brom Furane. Canzoneri and Oliveri. (17)

Equal weights of calcium hydrate and beta brom pyromucic acid are subjected to dry distillation. The distillate which is cloudy comes over at 100° and separates into a water layer and drops of brom furane. When a sufficient supply is obtained, the product is separated from the water and distilled over $CaCl_2$. It should boil at 103°. The yields are low, probably around 20%.

9. Action of Ammonia on Bromobenzene.

Although the problem at hand deals with bromofurane, it was decided first to try the Ullmann reaction on the analogous compound, bromobenzene.

5 g. bromobenzene and 3 g. dry NH_3 dissolved in 25 cc. of alcohol were heated in a sealed tube with 1 g. powdered copper. A temperature of 100-110° was maintained for 48 hours. Unchanged bromobenzene was then removed by steam distillation of the reaction mixture after acidification with dilute sulphuric acid. The mixture was then made alkaline and again steam distilled. The distillate was acidified with dilute sulphuric acid and evaporated nearly to dryness, giving crystals on cooling. When these were made alkaline, oily drops separated out, which had the odor of aniline. The amount was too small for a more complete indentification.

10. Attempt to Replace the Halogen of Bromofurane by the Amino Group.

2 g. of bromofurane were heated in a sealed tube with 1 g.

of powdered copper and an excess of dry NH_3 (4 g.) dissolved in 20 cc. of alcohol. A temperature of 100-120° was maintained for 30 hours. After cooling, the contents of the tube was filtered from copper and acidified with dilute sulphuric acid and steam distilled. Some of the original bromofurane appeared on adding water to the distillate. The residue in the flask was then made alkaline and again steam distilled, the distillate acidified with dilute sulphuric acid, and evaporated nearly to dryness in the hope that the amine sulphate might be obtained. This concentrated distillate was made strongly alkaline, but there was no indication of amino furane, since upon extracting the mixture with ether and evaporating, there was no oily residue from the extract.

V. SUMMARY

In the oxidation of furfural to pyromucic acid, the addition of ether to the mixture gives increased yields, probably due to the fact that the ether takes the furfural partly into solution in the water.

Pyromucic acid can be advantageously purified by heating the solution of the calcium salt with bone black. On acidification of such a clarified solution, pure white pyromucic acid separates out.

Pyromucic acid amide does not lend itself well to treatment by the Hofmann hypobromite reaction, since no amino furane was obtained by this method. The reaction was carried out repeatedly using different experimental conditions. This seems to be accounted for by the instability of the furane nucleus.

The furane ring is intermediate in characteristics between aromatic and aliphatic compounds, since it forms addition compounds with bromine, which easily split out HBr. The bromine atoms of tetra bromopyromucic acid, in the 1, 3, and 4 positions, are of practically the same reactivity as regards splitting out of HBr.

Although the furane nucleus is partly aliphatic in character, the analogy between alkyl halides and bromofurane ceases when it is attempted to replace the halogen of the latter by the amino group, since, as Werner has shown, this replacement will take place very easily even in the cold in the case of ethyl bromide. In this respect, bromofurane conducts itself suprisingly similarly to bromobenzene, which is very stable toward ammonia.

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(12) Canzoneri and Oliveri, Gazetta 16 487 (1886)

(13) Baum, Ber. 37 2951 (1904)

(14) Hill and Sanger, Ann. 232 67 (1885)

(15) See (14)

(16) Hill and Sanger, Ann. 232 58 (1885)

(17) Canzoneri and Oliveri, Gazetta 17 42 (1887)